PACKAGE INSERT TEMPLATE FOR CLOMIPHENE TABLET

Brand or Product Name
[Product name] Tablet 50mg

Name and Strength of Active Substance(s)

Clomiphene Citrate …mg equivalent to clomiphene ….mg

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)
eg White, circular flat beveled edge film-coated tablets marked '50' on one side

Pharmacodynamics

Clomiphene is a non-steroidal compound with weak estrogenic and moderate antiestrogenic properties. Clomiphene induces ovulation by increasing the output of pituitary gonadotropins. It binds competitively to estrogen receptors, decreasing the sites available to endogenous estrogen. The decreased binding of endogenous estrogen to hypothalamic and pituitary estrogen receptors results in increased secretion of luteinizing hormone-releasing hormone (LH-RH) and follicle-stimulating hormone-releasing hormone (FSH-RH) followed by the gonadotropins LH and FSH . In females, the gonadotropins stimulate maturation and endocrine activity of the ovarian follicle which is followed by the development and function of the corpus luteum.
In a hypothetical clomiphene induced ovulatory cycle resulting in successful ovulation, the initial endocrine event is an increase in LH and FSH levels. LH and FSH levels decline following discontinuation of clomiphene, but then surge at mid-cycle. Concomitantly, a sustained increase in estradiol is seen beginning with clomiphene administration and ending at a preovulatory peak. With successful ovulation, a substantial increase in progesterone levels is seen, indicating the formation of a functional corpus luteum .

Ovulation occurs 6 to 12 days after a course of therapy

Pharmacokinetics

Absorption
Clomiphene citrate is readily absorbed from the gastrointestinal tract.

Metabolism
It is metabolised in the liver and slowly excreted via the bile. Enterohepatic circulation occurs

Elimination
The majority of unchanged drug and its metabolites are excreted in the feces. The biological half-life is reported to be 5 days although traces are found in the faeces for up to 6 weeks. Appearance of the drug after 6 weeks suggests enterohepatic recirculation of the drug and metabolites. A small amount of unchanged drug and its metabolites is excreted in the urine and detectable for 6 weeks.

Indication

- Clomiphene citrate is indicated for the treatment of ovulatory failure.

- Clomiphene citrate is indicated only for patients in whom ovulatory dysfunction is demonstrated, who meet the conditions described in this prescribing information and for whom clomiphene is not contraindicated.

Other causes of infertility must be excluded or adequately treated before giving clomiphene citrate. Good levels of endogenous estrogen (as estimated from vaginal smears, endometrial biopsy, assay of urinary estrogen or endometrial bleeding in response to progesterone) provide a favorable prognosis for ovulatory response induced by clomiphene citrate. A low level of estrogen although clinically less favorable does not preclude successful outcome of therapy.
Clomiphene Citrate therapy is ineffective in patients with primary pituitary or primary ovarian failure. Clomiphene citrate therapy cannot be expected to substitute for specific treatment of other causes of ovulatory failure, such as thyroid or adrenal disorders.

Recommended Dosage

General Considerations:

The work-up and treatment of candidates for clomiphene citrate therapy should be supervised by physicians experienced in management of gynecologic or endocrine disorders. Patients should be chosen for therapy with clomiphene citrate only after careful diagnostic evaluation. The plan of therapy should be outlined in advance. Impediments to achieving the goal of therapy must be excluded or adequately treated before giving clomiphene citrate.

Many patients will respond to 50 mg daily for 5 days. In the determination of a recommended starting dose schedule, efficacy must be balanced against potential adverse effects. For example, the data available so far suggest that ovulation and pregnancy are slightly more attainable on 100 mg/day for 5 days than on 50 mg/day for 5 days.

As the dosage is increased, however, ovarian hyperstimulation and other adverse affects may be expected to increase. Furthermore, although the data do not yet establish a relationship between dosage and multiple births, it would seem reasonable on pharmacologic grounds that such a relationship does exist.

For these reasons, it would seem prudent to begin the treatment of the usual patient with a lower dose, 50 mg daily for 5 days, and to increase the dose only in those patients who do not respond to the first course. Special care with lower dosage or duration of treatment course is particularly recommended if unusual sensitivity to pituitary gonadotropin is suspected, such as in patients with polycystic ovary syndrome.

Recommended Dosage:

The recommended dose for the first course of clomiphene citrate is 50 mg daily for 5 days.

Therapy may be started at any time in the patient who has had no recent uterine bleeding. If progestin-induced bleeding is planned, or if spontaneous uterine bleeding occurs before therapy, the regimen of 50 mg daily for 5 days should be started on or about the fifth day of the cycle. When ovulation occurs at this dosage, there is no advantage to increasing the dose in subsequent cycles of treatment.

If ovulation appears not to have occurred after the first course of therapy, a second course of 100 mg daily (two 50 mg tablets given as a single daily dose) for 5 days should be given. This course may be started as early as 30 days after the previous one.

Increase of the dosage or duration of therapy beyond 100 mg/day for 5 days should not be undertaken.

The majority of patients who are going to respond will respond to the first course of therapy, and 3 courses should constitute an adequate therapeutic trial. If ovulatory menses have not yet occurred, the diagnosis should be re-evaluated. Treatment beyond this is not recommended in the patient who does not exhibit evidence of ovulation.

Pregnancy:

The importance of properly timed coitus cannot be overemphasized. For regularity of cyclic ovulatory response it is also important that each course of clomiphene citrate be started on or about the fifth cycle day, once ovulation has been established.

As with other therapeutic modalities, clomiphene citrate therapy follows the rule of diminishing returns, such that likelihood of conception diminishes with each succeeding course of therapy. Before starting treatment, patients should be advised of the possibility of multiple pregnancy and its potential hazards if conception occurs in relationship to clomiphene citrate therapy.

Long-term cyclic therapy not recommended:

Since the relative safety of long term cyclic therapy has not yet been conclusively demonstrated and since the majority of patients will ovulate following 3 courses long-term cyclic therapy is not recommended, i.e. beyond a total of about 6 cycles (including 3 ovulatory cycles).

Mode of Administration
Oral

Contraindications

- Pregnancy
- Uncontrolled thyroid or adrenal dysfunction
- Liver disease or a history of liver dysfunction
- Abnormal uterine bleeding
- Endometrial carcinoma
- Hormone dependent tumors
- Ovarian cysts
- Organic intracranial lesion
- Hypersensitivity to clomiphene

Warnings and Precautions
Clomiphene should not be used in patients with pre-existing mental depression or thrombophlebitis because of the risk of exacerbation.

Ovarian hyperstimulation syndrome and abnormal ovarian enlargement may occur, lowest dose is suggested to minimize this complication

Ovarian cyst: Pelvic examination is necessary prior to start of and before each subsequent course of clomiphene citrate treatment. Clomiphene citrate should not be given in the presence of an ovarian cyst (including endometriosis involving the ovary) except polycystic ovary since further enlargement of the cyst may occur. The lowest doses possible should be used to minimise ovarian enlargement or cyst formation; some patients with polycystic ovary syndrome may have

an exaggerated response to usual doses of clomiphene. Patients should be instructed to report any abdominal or pelvic pain, distension, or weight gain, as this may indicate the presence or enlargement of ovarian cysts. They should also be evaluated for the presence of ovarian cysts before each cycle of treatment. If abnormal enlargement occurs, clomiphene should not be given until the ovaries have returned to pre-treatment size, and subsequent doses should be reduced.

Clomiphene should be used with caution in patients with uterine fibroids, due to the potential for enlargement of the fibroids.

Multiple pregnancies: There is an increased chance of multiple pregnancies when conception occurs in relationship to clomiphene citrate therapy. The potential complications and hazards of multiple pregnancies should be discussed with the patient.

Pregnancy wastage and birth anomalies: The patient should be informed of the greater pregnancy risks associated with certain characteristics or conditions of any pregnant woman: e.g., age of female and malepartner, history of spontaneous abortions, Rh genotype, abnormal menstrual history, infertility history (regardless of cause), organic heart disease, diabetes, exposure to infectious agents such as rubella, familial history of birth anomaly, and other risk factors that may be pertinent to thepatient for whom clomiphene citrate is being considered. Based upon the evaluation of the patient, genetic counselling may be indicated.

Visual symptoms: Patients should be advised that blurring or other visual symptoms may occasionally occur during or shortly after therapy with clomiphene citrate. The significance of these visual symptoms is not understood. If the patient has any visual symptoms, treatment should be discontinued and complete ophthalmologic evaluation performed.

Long-term cyclic therapy is not recommended, because of the uncertainty regarding increased risk of ovarian cancer: a maximum of 6 cycles of treatment has generally been advised

Effects on the ability to drive and use machines

Patients should be warned that visual symptoms may render such activities as driving a car or operating machinery more hazardous than usual, particularly under conditions of variable lighting.

Interactions with Other Medicaments

None known / No information available

Updated November 2012

Statement on Usage During Pregnancy and Lactation

Pregnancy

Clomiphene use is contraindicated during pregnancy. Prior to administration of each cycle of clomiphene treatment, pregnancy should be ruled out.

Lactation

Lactation studies with clomiphene have not been conducted in humans, and it is not known whether it is excreted into human milk. Clomiphene may reduce lactation in some nursing women. Caution should be exercised when administering clomiphene to a nursing woman

Adverse Effects / Undesirable Effects

- The incidence and severity of adverse effects of clomiphene citrate tend to be related to the dose used.

Common

- Cardiovascular: Syncope
- Dermatologic: Acne, Dermatitis,Dry hair , Erythema, Erythema multiforme, Erythema nodosum, Vasomotor Flushes, Hypertrichosis, Loss of hair Pruritus, Rash , Urticaria
- Endocrine metabolic: Disorder of thyroid gland, Weight decreased , Weight increased
- Gastrointestinal: Abdominal-pelvic discomfort (distention, bloating), acute abdominal pain, Constipation ,Diarrhea , Gastrointestinal tract finding , Increased appetite ,) nausea and vomiting
- Hepatic: Increased liver enzymes
- Musculoskeletal: Arthralgia, Backache, Myalgia
- Neurologic: Asthenia, Dizziness , Headache ,Insomnia, Lightheadedness , Migraine, Paresthesia, Unsteady when walking, Vertigo
- Ophthalmic: Eye / vision finding, temporary functional visual loss, Pain in eye, Photopsia
- Otic: Tinnitus
- Psychiatric: Anxiety, Depression, Fatigue , Feeling nervous , Irritability, Mood disorder
- Renal: Polyuria
- Reproductive: Cyst of ovary, Endometriosis, Hyperstimulation of ovaries, Pain of breast Urogenital finding, Vaginal dryness
- Other: Fever

Serious

Updated November 2012

- Cardiovascular: Cardiac dysrhythmia, Chest pain, Edema, Hypertension, Palpitations, Phlebitis, Pulmonary embolism, Tachycardia
- Endocrine metabolic: Gynecomastia
- Gastrointestinal: Pancreatitis, acute
- Hematologic: Leukocytosis, Thrombophlebitis
- Hepatic: Hepatitis, Liver carcinoma
- Neurologic: Cerebrovascular accident, Neoplasm of nervous system, Seizure
- Ophthalmic: Cataract, Macular retinal edema, Optic neuritis, Posterior vitreous detachment, Retinal hemorrhage, Retinal vascular disorder, Thrombosis of retinal artery, Thrombosis of retinal vein
- Psychiatric: Psychotic disorder
- Reproductive: Disorder of menstruation, Ectopic pregnancy, Endometrial carcinoma, Gestational trophoblastic neoplasm, Hemorrhagic cyst of ovary, Hypertrophy of ovary, Neoplasm of ovary, Ovarian cancer, Testicular cancer, Tubal pregnancy, Uterine hemorrhage
- Other: Carcinoma of breast, Fetal neoplasm, Gestational trophoblastic neoplasm, Malignant neoplasm of liver, Neoplasm of breast, Neoplasm of endometrium, Neoplasm of nervous system, Neoplasm of ovary

Ovarian Enlargement: At recommended dosage, abnormal ovarian enlargement is infrequent, although the usual cyclic variation in ovarian size may be exaggerated. Similarly, cyclic pain (mittelschmerz) may be accentuated. With higher or prolonged dosage, more frequent ovarian enlargement and cyst formation may occur, and the luteal phase of the cycle may be prolonged.

Overdose and Treatment

Symptoms

Mild to moderate toxicity: Includes flushing abdominal pain, ovarian enlargement, pelvic pain, nausea, vomiting, visual blurring, spots or flashes, and scotomata. Mild ovarian hyperstimulation symptoms include nausea, vomiting, diarrhea, and weight gain.

Severe toxicity: Severe ovarian hyperstimulation syndrome may include gross ovarian enlargement, ascites, dyspnea, oliguria, pleural effusion, pericardial effusion, anasarca, acute abdominal pain, hypotension, renal failure, pulmonary edema, intraperitoneal and ovarian hemorrhage, ovarian torsion, deep venous thrombosis, respiratory distress, electrolyte imbalances, hypovolemia, hypoproteinemia, hemoconcentration, and shock.

Maximal enlargement of the ovary may not occur until several days after discontinuation of the course of clomiphene citrate. Female patients of reproductive age who have taken an overdose should be observed for 2 or 3 weeksfor ovarian enlargement.

Treatment
Most exposures are mild and require only supportive care. In severe toxicity, support respiratory and cardiovascular function as needed. For patients with severe ovarian hyperstimulation syndrome, initiate intravenous hydration, monitor fluid input and output, and initiate deep venous thrombosis prophylaxis.

Storage Conditions
[eg Store below….°C]

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]